Amendments to the Specification:

Kindly amend the Brief Description of the Drawings, which begins on page 12, line 1, as follows:

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 (SEQ ID NOS:125-126) shows the nucleotide sequence of the human pituitary-derived G protein-coupled receptor protein cDNA fragment harbored in cDNA clone p19P2 isolated by PCR using human pituitary-derived cDNA and the amino acid encoded by the nucleotide sequence. The primer used for sequencing was -21M13. The underscored region correspond to the synthetic primer.

FIG. 2 (SEQ ID NOS:127-128) shows the nucleotide sequence of the human pituitary-derived G protein-coupled receptor protein cDNA fragment harbored in cDNA clone p19P2 isolated by PCR using human pituitary-derived cDNA and the amino acid sequence encoded thereby. The primer used for sequencing was M13RV-N (Takara). The underscored region correspond to the synthetic primer.

FIG. 3 shows a partial hydrophobic plot of the protein encoded by the human pituitary-derived G protein-coupled receptor protein cDNA fragment harbored in p19P2 constructed according to the amino acid sequence shown in FIG. 1.

FIG. 4 shows a partial hydrophobic plot of the protein encoded by the human pituitary-derived G protein-coupled receptor protein cDNA fragment harbored in p19P2 constructed according to the amino acid sequence shown in FIG. 2.

FIG. 5 (SEQ ID NOS:129-130) is a diagram comparing the partial amino acid sequence of the

protein encoded by the human pituitary-derived G protein-coupled receptor protein cDNA fragment harbored in p19P2 as shown in FIGS. 1 and 2 with the known G protein-coupled receptor protein S12863. The shadowed region represents the region of agreement. The 1 to 9 amino acid sequence of p19P2 corresponds to the 1 to 99 amino acid sequence of FIG. 1 and the 156 to 230 amino acid sequence corresponds to the 1 to 68 amino acid sequence of FIG. 2.

FIG. 6 (SEQ ID NOS:99-100) shows the nucleotide sequence of the MIN6-derived G protein-coupled receptor protein cDNA fragment based on the nucleotide sequences of the MIN6-derived G protein-coupled receptor protein cDNA fragments harbored in the cDNA clones pG3-2 and pG1-10 isolated by PCR using MIN6-derived cDNA and the amino acid sequence encoded by the nucleotide sequence. The underscored region correspond to the synthetic primer.

FIG. 7 (SEQ ID NOS:101-102) is a diagram comparing the partial amino acid sequence encoded by pG3-2/pG1-10 of the MIN6-derived G protein-coupled receptor protein shown in FIG. 6 with the partial amino acid sequence of the protein encoded by p19P2 shown in FIGS. 1 and 2. The shadowed region corresponds to the region of agreement. The 1 to 99 amino acid sequence of the protein encoded by p19P2 corresponds to the 1 to 99 amino acid sequence of FIG. 1 and the 156 to 223 amino acid sequence corresponds to the 1 to 68 amino acid sequence of FIG. 2. The 1 to 223 amino acid sequence of the protein encoded by pG3-2/pG1-10 corresponds to the 1 to 223 amino acid sequence of FIG. 6.

FIG. 8 is a partial hydrophobic plot of the MIN6-derived G protein-coupled receptor protein constructed according to the partial amino acid sequence shown in FIG. 6.

FIG. 9 (SEQ ID NOS:103-104) shows the entire nucleotide sequence of the human pituitary-derived G protein-coupled receptor protein cDNA harbored in the cDNA clone phGR3 isolated from a human pituitary-derived cDNA library by the plaque hybridization method using the DNA fragment inserted in p19P2 as a probe and the amino acid sequence encorded by the nucleotide

sequence.

FIG. 10 shows the result of Northern blotting of human pituitary mRNA hybridized with radioisotope-labeled human pituitary cDNA clone phGR3.

FIG. 11 shows a hydrophobic plot of the protein encoded by the human pituitary-derived G protein-coupled receptor protein cDNA harbored in the phGR3 as constructed according to the amino acid sequence shown in FIG. 9.

FIG. 12 (SEQ ID NOS:105-106) shows the nucleotide sequence of the MIN6-derived G protein-coupled receptor protein cDNA fragment harbored in the cDNA clone p5S38 isolated by PCR using MIN6-derived cDNA and the amino acid sequence encoded by the nucleotide sequence. The underscored region correspond to the synthetic primer.

FIG. 13 (SEQ ID NOS:107-108) shows a diagram comparing the partial amino acid sequence of MIN6-derived G protein-coupled receptor protein encoded by p5S38 shown in FIG. 12 with the partial amino acid sequence of G protein-coupled receptor protein encoded by the cDNA fragment harbored in p19P2 as shown in FIGS. 1 and 2 and the partial amino acid sequence of G protein-coupled receptor protein encoded by the nucleotide sequence generated from the nucleotide sequences of cDNA fragments contained in pG3-2 and pG1-10 shown in FIG. 6. The shadowed region represents the sequence region of agreement. The 1 to 144 amino acid sequence of the protein encoded by p5S38 corresponds to the 1 to 144 amino acid sequence of FIG. 12, the 1 to 99 amino acid sequence of the protein encoded by p19P2 corresponds to the 1 to 99 amino acid sequence of FIG. 1 and the 156 to 223 amino acid sequence corresponds to 1 to 68 amino acid sequence of FIG. 2. The 1 to 223 amino acid sequence of the protein encoded by pG3-2/pG1-10 corresponds to the 1 to 223 amino acid sequence of FIG. 6.

FIG. 14 shows a partial hydrophobic plot of the protein encoded by the MIN6-derived G protein-

coupled receptor protein cDNA harbored in p5S38 as constructed according to the partial amino acid sequence shown in FIG. 12.

FIG. 15 shows the results of the following analysis. Thus, RT-PCR was carried out to confirm the expression of mRNA in CHO cells transfected by PAKKO-19P2. Lanes 1-7 represent the results obtained by performing PCRs using serial dilutions of pAKKO-19P2 for comparison, i.e. the 10 μl/ml stock solution (lane 1), 1/2 dilution (lane 2), 1/4 dilution (lane 3), 1/64 dilution (Lane 4), 1/256 dilution (lane 5), 1/1024 dilution (lane 6), and 1/4096 dilution (lane 7) of the plasmid as templates, and analyzing the reaction mixtures by 1.2% agarose gel electrophoresis. Lanes 8 through 11 are the results obtained by performing PCRs using a 1/10 dilution (lane 8), a 1/100 dilution (lane 9), and a 1/1000 dilution (lane 10) of the cDNA prepared from the CHO-19P2 cell line as templates and subjecting the respective reaction mixtures to electrophoresis. Lane 11 was obtained by performing PCR using a template obtained by carrying out cDNA synthesis without reverse transcriptase and subjecting the PCR reaction product to electrophoresis. Lanes 12 and 13 were obtained by performing PCR using cDNAs prepared from mock CHO cells with and without addition of reverse transcriptase, respectively, as templates and subjecting the respective reaction products to electrophoresis. M represents the DNA size marker. The lanes at both ends were obtained by electrophoresing 1 μl of .lambda./Sty I digest (Nippon Gene) and the second lane from right was obtained with 1 μl of .o slashed./.chi.174/Hinc II digest (Nippon Gene). The arrowmark indicates the position of the band amplified by PCR of about 400 bp.

FIG. 16 shows the activity of the crude ligand peptide fraction extracted from rat whole brain to promote release of arachidonic acid metabolites from CHO-19P2 cells. The arachidonic acid metabolite releasing activity was expressed as % of the amount of [^{3} H] arachidonic acid metabolites released in the presence of the crude ligand polypeptide fraction with the amount of [^{3} H] arachidonic acid metabolites released in the presence of 0.05% BAS-HABB being taken as 100%. The activity to promote release of arachidonic acid metabolites from the CHO-19P2 cell

line was detected in a 30% CH_3CN fraction.

FIG. 17 shows the activity of the crude ligand polypeptide fraction extracted from bovine hypothalamus to promote release of arachidonic acid metabolites from CHO-19P2 cells. The arachidonic acid metabolite release-promoting activity was expressed as % of the amount of [^{3} H] arachidonic acid metabolites released in the presence of the crude ligand polypeptide fraction with the amount of [^{3} H] arachidonic acid metabolites released in the presence of 0.05% BAS-HABB being taken as 100%. The activity to promote release of arachidonic acid metabolites from the CHO-19P2 cell line was detected in a 30% CH_3CN fraction just as in the crude ligand polypeptide fraction from rat whole brain.

FIG. 18 shows the activity of the fraction purified with the reversed-phase column C18 218TP5415 to specifically promote release of arachidonic acid metabolites from CHO-19P2 cells. The active fraction from RESOURCE S was fractionated on C18 218TP5415. Thus, chromatography was carried out at a flow rate of 1 ml/min. on a concentration gradient of 20%-30% CH_3 CN/0.1% TFA/H_2 O, the eluate was collected in 1 ml fractions, and each fraction was lyophilized. Then, the activity of each fraction to specifically promote release of arachidonic acid metabolites from the CHO-19P2 cell line was determined. As a result, the activity was fractionated into 3 fractions (designated, in the order of elution, as P-1, P-2, and P-3).

FIG. 19 shows the activity of the fraction purified with the reversed-phase column diphenyl 219TP5415 to specifically promote arachidonic acid metabolite release from CHO-19P2 cells. The P-3 active fraction from C18 218TP5415 was fractionated on diphenyl 219TP5415. The chromatography was carried out at a flow rate of 1 ml/min. on a concentration gradient of 22%-25% CH_3 CN/0.1% TFA/H_2 O, the eluate was collected in 1 ml fractions, and each fraction was lyophilized. Then, the activity to specifically promote release of arachidonic acid metabolites from CHO-19P2 cells in each fraction was determined. As a result, the activity converged in a single peak.

FIG. 20 shows the activity of the fraction purified by reversed-phase column μRPC C2/C18 SC 2.1/10 to specifically promote release of arachidonic acid metabolites from CHO-19P2 cells. The peak active fraction from diphenyl 219TP5415 was fractionated on μRPC C2/C18 SC 2.1/10. The chromatography was carried out at a flow rate of 100 μl/min. on a concentration gradient of 22%-23.5% CH_3 CN/0.1% TFA/H_2 O, the eluate was collected in 100 μl fractions, and each fraction was lyophilized. Then, the activity to specifically promote release of arachidonic acid metabolites from CHO-19P2 cells in each fraction was determined. As a result, the activity was found as two peaks of apparently a single substance (peptide).

FIG. 21 shows the activity of the P-2 fraction purified by reversed-phase column μRPC C2/C18 SC 2.1/10 to specifically promote release of arachidonic acid metabolites from CHO-19P2 cells. The chromatography was carried out at a flow rate of 100 μl/min. on a concentration gradient of 21.5%-23.0% CH_3 CN/0.1% TFA/dH_2 O, the eluate was collected in 100 μl fractions, and each fraction was lyophilized. Then, the activity to specifically promote release of arachidonic acid metabolites from CHO-19P2 cells in each fraction was determined. As a result, the activity was found as a peak of apparently a single substance.

FIG. 22 (SEQ ID NOS:110-111) shows the nucleotide sequence of bovine hypothalamus ligand polypeptide cDNA fragment as derived from the nucleotide sequence of the bovine hypothalamus-derived ligand polypeptide cDNA fragment which specifically promotes release of arachidonic acid metabolites from CHO-19P2 cells as harbored in a cDNA clone isolated by PCR using bovine hypothalamus-derived cDNA and the amino acid sequence encoded by said nucleotide sequence. The region indicated by the arrowmark corresponds to the synthetic primer.

FIG. 23 (SEQ ID NOS:112-113) shows the nucleotide sequence of the bovine hypothalamus-derived ligand polypeptide cDNA fragment generated according to the nucleotide sequence of the bovine hypothalamus-derived ligand polypeptide cDNA fragment which specifically promotes

release of arachidonic acid metabolites from CHO-19P2 cells as harbored in a cDNA clone isolated by PCR using bovine hypothalamus-derived cDNA and the amino acid sequence encoded by said nucleotide sequence. The region indicated by the arrowmark corresponds to the synthetic primer.

FIG. 24 (SEQ ID NOS:114-117) shows the amino acid sequences (a) and (b) of the bovine hypothalamus-derived ligand polypeptides which specifically promote release of arachidonic acid metabolites from CHO-19P2 cells and the cDNA sequence coding for the full coding region of the ligand poly-peptides defined by SEQ ID NO:1 and SEQ ID NO:44.

FIG. 25 shows the concentration-dependent activity of synthetic ligand polypeptide (19P2-L31) to specifically promote release of arachidonic acid metabolites from CHO-19P2 cells. The synthetic peptide was dissolved in degassed dH_2O at a final concentration of 10^{-3} M and diluted with 0.05% BSA-HBSS to concentrations of 10^{-12} M-10^{-6} M. The arachidonic acid metabolite releasing activity was expressed in the measured radioactivity of [^{3} H] arachidonic acid metabolites released in the supernatant when the dilution was added to the cells. As a result, the activity of 19P2-31 to specifically promote release of arachidonic acid metabolites from CHO-19P2 cells was found in a concentration-dependent manner.

FIG. 26 shows the concentration-dependent activity of synthetic ligand polypeptide (19P2-L31(O)) to specifically promote release of arachidonic acid metabolites from CHO-19P2 cells. The synthetic ligand peptide was dissolved in degassed dH_2O at a final concentration of 10^{-3} M and diluted with 0.05% BSA-HBSS to concentrations of 10^{-12} M-10^{-6} M. The arachidonic acid metabolite releasing activity was expressed in the measured radioactivity of [^{3} H] arachidonic acid metabolites released in the supernatant when the dilution was added to the cells. As a result, the activity of 19P2-L31(O) to specifically promote release of arachidonic acid metabolites from CHO-19P2 cells was found in a dose-dependent manner.

FIG. 27 shows the activity of synthetic ligand polypeptide 19P2-L20 to specifically promote release of arachidonic acid metabolites from CHO-19P2 cells. The synthetic peptide was dissolved in degassed dH_2O at a final concentration of 10^{-3} M and diluted with 0.05% BSA-HBSS to concentrations of 10^{-12} M-10^{-6} M. The arachidonic acid metabolite releasing activity was expressed in the measured radioactivity of [^{3} H] arachidonic acid metabolites released in the supernatant when the dilution was added to the cells. As a result, the activity of 19P2-L20 to specifically promote release of arachidonic acid metabolites from CHO-19P2 cells was found in a dose-dependent manner.

FIG. 28 shows the 1.2% agarose gel electrophoregram of the DNA fragments of the phages cloned from a bovine genomic library as digested with restriction enzymes BamHI(B) and SalI(S). As the DNA size marker (M), StyI digests of .lambda. phage DNA were used. In lane B, two bands derived from the vector were detected in positions between the first (19,329 bp) and second (7.743 bp) marker bands, as well as 3 bands derived from the inserted fragment between the third (6,223 bp) and 5th (3,472 bp) bands. In lane S, two bands derived from the vector were similarly detected but due to the overlap of the band of the inserted fragment, the upper band is thicker than the band in lane B.

FIG. 29 (SEQ ID NO:118) shows the nucleotide sequence around the coding region as decoded from bovine genomic DNA. The 1st to 3rd bases (ATG) correspond to the translation start codon and the 767th to 769th bases (TAA) correspond to the translation end codon.

FIG. 30 (SEQ ID NO:119-120) shows a comparison between the nucleotide sequence (genome) around the coding region as deduced from bovine genomic DNA and the nucleotide sequence (cDNA) of bovine cDNA cloned by PCR. The sequence region of agreement is indicated by shading. As to the 101st to 572nd region, there is no corresponding region in the nucleotide sequence of cDNA, indicating that it is an intron.

FIG. 31 (SEQ ID NOS:121-122) shows the translation of the amino acid sequence encoded after elimination of the intron from the nucleotide sequence around the coding region as decoded from bovine genomic DNA.

FIG. 32 (SEQ ID NOS:123-124) shows the full-length amino acid sequence and the cDNA sequence coding for the full coding region of rat ligand polypeptide.

FIG. 33 (SEQ ID NOS:131-135) shows amino acid sequence of bovine ligand polypeptide and the nucleotide sequences of DNAs coding for bovine polypeptide and rat polypeptide. The arrowmark indicates the region corresponding to the synthetic primer.

FIG. 34 (SEQ ID NOS:134-135) shows the full-length amino acid sequence and the sequence of cDNA coding for the full coding region of human ligand polypeptide.

FIG. 35 (SEQ ID NO:136-138) shows a comparison of the amino acid sequences in the translation region of bovine ligand polypeptide, rat ligand polypeptide, and human ligand polypeptide.

FIG. 36 shows the results of receptor binding experiments on living cells wherein radioiodinated ligand polypeptide is used in the experiments.

FIG. 37 shows the results of measurements of release of arachidonic acid metabolites from CHO-19P2-9 and CHO-UHR1 by ligand polypeptide.

FIG. 38 shows the results of quantification of UHR-1 mRNA by RT-PCR in discrete regions of the brain and tissues in rats.

FIG. 39 shows the results of quantification of ligand polypeptide mRNA by RT-PCR in discrete

regions of the brain and tissues in rats.

FIG. 40 shows effects of ligand polypeptide on glucose-induced increase in plasma insulin concentration, which is measured by radioimmunoassay.

FIG. 41 shows the results of measurements of motor activity by administration of 10 nmol of ligand polypeptide to mouse.

(a) relates to spontaneous motor activity and (b) relates to rearing.

FIG. 42 shows the results of measurements of motor activity by administration of 1 nmol of ligand polypeptide to mouse.

(a) relates to spontaneous motor activity and (b) relates to rearing.

FIG. 43 shows the results of measurements of motor activity by administration of 0.1 nmol of ligand polypeptide to mouse.

(a) relates to spontaneous motor activity and (b) relates to rearing.

FIG. 44 shows the results of measurements of motor activity by administration of 0.01 nmol of ligand polypeptide to mouse.

(a) relates to spontaneous motor activity and (b) relates to rearing.

FIG. 45 shows the results of measurements of body temperature which is measured at the time when the ligand polypeptide is administered to the lateral ventricle of mice. The administration of ligand polypeptide is carried out after 15 hours from administration of reserpine at a dose of 3

mg/kg, S.C.

In FIG. 45, the single star mark asterisk shows $p<0.05$ and the double star marks asterisks shows $p<0.01$.

FIG. 46 illustrates the drawing in which the micro-injection cannula is inserted into the area postrema at an angle of 20°.

FIG. 47 shows the typical example of direct and average blood pressure which is measured after the injection of ligand polypeptide into the area postrema of rat. It is measured after the injection of 10 nmol of ligand polypeptide at the rate of 1 μl/min, and under the condition of non-anesthesia.

FIG. 48 shows the results of measurements of growth hormone (GH) in plasma when 50 nmol of ligand polypeptide is administered into the third ventricle of rat after anesthesia by pentobarbital.

FIG. 49 shows the changes of secretion of GH in plasma by administration of 50 nmol of ligand polypeptide into the third ventricle in freely moving rats.

The ligand polypeptide or PBS was administered into the third ventricle. At 10 min later, 5 μg/kg of GHRH was administered intravenously to the rat conscious. GH levels were measured just prior to intraventricular administration (time 0) and 10, 20, 30, 40, and 60 min after the intravenous injection of GHRH.

In FIG. 49, the single star mark asterisk shows $p<0.05$ and the double star marks asterisks show $p<0.01$.

FIG. 50 shows the relationship between the ligand polypeptide serum and the absorbance.

FIG. 51 shows the inhibition of the release of archidonic acid metabolites by anti-ligand polypeptide polyclonal antibody.

FIG. 52 (SEQ ID NOS:139-140) shows the sequence of cDNA coding for UHR-1, which is constructed on pAKKO-UHR1-7.

Kindly amend the paragraph starting on line 9 of page 124, as follows:

1) Synthesis of Ser-Arg-Ala-His-Gln-His-Ser-Met-Glu-Ile-Arg-Thr-Pro-Asp-Ile-Asn-Pro-Ala-Trp-Tyr-Ala-Gly-Arg-Gly-Ile-Arg-Pro-Val-Gly-Arg-Phe-NH_2 (19P2-L31) (SEQ ID NO 97)

Kindly amend the paragraph starting on line 12 of page 125, as follows:

2) Synthesis of Ser-Arg-Ala-His-Gln-His-Ser-Met-Glu-Ile-Arg-Thr-Pro-Asp-Ile-Asn-Pro-Ala-Trp-Tyr-Ala-Gly-Arg-Gly-Ile-Arg-Pro-Val-Gly-Arg-Phe-NH_2 (19P2-L31) (SEQ ID NO 97)

Kindly amend the paragraph starting on line 11 of page 126, as follows:

Synthesis of Ser-Arg-Ala-His-Gln-His-Ser-Met-Glu-Ile-Arg-Thr-Pro-Asp-Ile-Asn-Pro-Ala-Trp-Tyr-Ala-Gly-Arg-Gly-Ile-Arg-Pro-Val-Gly-Arg-Phe-NH_2 (19P2-L31) (SEQ ID NO 97)

Kindly amend the paragraph starting on line 31 of page 126, as follows:

Synthesis of Thr-Pro-Asp-Ile-Aln-Pro-Ala-Trp-Tyr-Ala-Gly-Arg-Gly-Ile-Arg-Pro-Val-Gly-Arg-Phe-NH_2 (19P2-L20) (SEQ ID NO 98)